the system. Given the central role that multibody dynamics plays in the presented framework, a suite of Generalized Divide-and-Conquer Algorithms-based approaches is employed to this end, since these methods offer a good combination of computational efficiency and modular structure. The computational complexity of the algorithm is *O(n)* and *O(logn)* in serial and parallel implementations, respectively, where denotes the number of degrees of freedom of the system.

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Keep it Flexible: Driving Macromolecular Rotary Motions in Atomistic Simulations with Gromacs

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Biomolecular function is often performed through motions of subunits. Rotary motions, in particular, are essential for the function of many motor proteins. Rotary mechanisms have been demonstrated, e.g., for the Fo and F1 motors in F-ATP synthase, and for the bacterial flagellar motor. The molecular mechanisms by which chemical reactions or transmembrane gradients drive protein rotary motions are in most cases not understood in full detail. Moreover, these motions are typically too slow or infrequent to be accessible to equilibrium molecular dynamics simulations. To overcome these limitations, external forces or torques can be imposed on specific subunits to induce rotation or to increase its rate. Using a simple fixed axis rotation, however, does not reflect situations such as F1-ATP synthase, where the rotating part is flexible and adapts to the steric restraints of its bearing. To more realistically describe biomolecular rotations, we have developed a new technique that allows for flexible adaptions of both the rotary subunit as well as the local rotation axis during the simulation. For the example of gamma subunit rotation in F1-ATP synthase, we show that the flexible rotation method imposes minimal constraints on the rotor and allows for conformational adaptions to the surrounding. This is confirmed by a fivefold reduced torque when using our flexible axis compared to a fixed axis rotation at the same rotation rate. The flexible axis technique can be used, e.g., to mimic rotary molecular motors, to restrain the orientation of a protein or ligand, or, in combination with umbrella sampling, to calculate the preferred orientation of transmembrane proteins within a lipid bilayer.

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A Multiscale Simulation Approach to Small Ligand Diffusion in Proteins: Application to Mutant [NiFe]-Hydrogenases

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Hydrogenases are enzymes that efficiently catalyze the reversible conversion of hydrogen molecules (H_2) to protons and electrons. In recent years they have attracted much interest due to their potential as catalysts for biofuel cells. One major problem in applications is their inhibition by O_2 and CO molecules. To overcome this problem, it is necessary to understand the underlying mechanism of gas diffusion on a molecular level. In this work, we present a novel method for the calculation of gas diffusion rates in proteins and apply the method to H_2 and CO transport in V74M L122M, V74M L122A, and V74M mutant [NiFe]-hydrogenases. The results are compared with experiment and our previously computed rates for the wildtype (WT) enzyme. We find that the diffusion rates for H_2 are similar in V74M and WT hydrogenases, but the diffusion rates for CO in the mutants are lower than in the WT enzyme. The latter finding agrees well with experimentally-determined on-rates, which as a whole shows different levels of mutation effect. It is another example that our methodology can be applied not only to the wildtype enzyme but also to mutants, once the majority of the microscopic rates are obtained from the wildtype equilibrium simulations. According to our calculations, the mutation effect on the rates can be due to multiple combinations of structural parameters in different mutants. This finding is unexpected and can explain why the slowest microscopic transition rates are in the micro-second time regime. In addition to the known 'control point' motif, Val74-Leu122, from our results we also confirm that the Val74-Arg476 motif proposed in our previous work is a second bottleneck for gas diffusion.

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Protein Force Field Improved by using a New Backbone-Torsion-Energy Term

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Bimolecular simulations are performed by using potential energy functions with force-field parameters such as AMBER, CHARMM, OPLS, GROMOS, and ECEPP. We have performed detailed comparisons of three version of AMBER (ff94, ff96, and ff99), CHARMM22, OPLS-AA/L, and GROMOS96 by generalized-ensemble simulations of two small peptides [1]. As results of these comparisons, we saw that these force fields showed clearly different behavior of peptides, especially, about secondary-structure-forming tendencies. These results imply that it is necessary to refine and improve the existing force-field parameters. Among the energy terms, the torsion-energy term is the most problematic. We have proposed force-field refinement methods. This method consists of minimizing the sum of the square of the force acting on each atom in the proteins with the structures from the Protein Data Bank (PDB) [2]. Additionally, we also proposed a new backbone-torsion-energy term, which is represented by a double Fourier series in two variables, the backbone dihedral angles phi and psi [3,4].

In this poster, we apply our optimization method and backbone-torsion-energy term to AMBER ff94(ff96) force field for molecular simulation of protein systems. The result implies that the new force-field parameters give structures of two peptides more consistent with the experimental implications for the secondly-structure-forming tendencies than the original force field.

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Replica Exchange of Self-Guided Langevin Dynamics Simulation

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Based on the self-guided Langevine dynamics (SGLD) simulation method, this work presents a guiding effect based replica exchange method (RXSGLD). The key characteristic of this method is that it can be performed at constant temperature to achieve high replica exchange efficiency. By avoiding temperature elevation, this method has a higher replica exchange efficiency for large systems and uses relatively fewer replicas compared with temperature based replica exchange methods. This method is made possible through recent progress in the understanding of the conformational distribution in SGLD simulations. The partition function of the SGLD ensemble provides a quantitative relation for the calculation of exchange probabilities between replicas. RXSGLD can be utilized as an alternative to the force-momentum based self-guided Langevin dynamics (SGLDfp) to directly sample canonical ensemble without reweighting. This method can be combined with the temperature-based replica exchange method to further improve conformational search efficiency. Using skewed double well systems, we demonstrate that RXSGLD produces correct ensemble distributions while accelerating statistical convergence. Through β-hairpin folding simulations with implicit and explicit solvent, we demonstrate that RXSGLD has excellent conformational search efficiency and can be applied to large systems, while preserving the ensemble distribution.

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An Induced-Fit Docking Method for Refining Drug-Receptor Interactions Derived from Maxwellian-Assessor Nanoprobes (Quantum Mechanics-Based Criterion Assessment) Placed Over Adaptive Intervals of Molecular Dynamics Sampling

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Herein, we present a novel method for final assessment and/or enrichment of high-throughput virtual screening (HTVS) campaigns. After exhaustive sampling of ligand rotor-bonds and individual docking poses has culled the millions of compounds down to a final set of 100 ligands, the current state of art docking programs (HTVS) still require an improved ranking-assessment tool to optimize ligands to better approximate crystallographic position. Here, we present a method to apply a Maxwellian-based criterion assessment that utilizes